Weight of Evidence for the Neurotoxicity of Perchloroethylene

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Abstract:

Perchloroethylene (perc) has been demonstrated to have effects on neural function in both animals and humans. This presentation summarizes the literature on neurological testing of people exposed to perc occupationally in dry cleaning facilities and on people living near dry cleaning facilities. It also summarizes the structural and functional studies of laboratory animals exposed to perc via inhalation and other routes of exposure. The weight of evidence for neurotoxicity is presented for both acute and chronic exposures scenarios affecting numerous domains of neurological function including visual, motor and cognitive is presented. The animal database is limited in that no studies have evaluated cognitive function after chronic exposure as would be indicated by findings in humans. Developmental neurotoxicity following exposure to perc has not been examined in any systematic fashion. Some studies suggest effects (e.g, visual and motor functional deficits) on the nervous system following developmental exposure. The range of effects in humans chronically exposed via inhalation includes LOAELs ranging from 0.3 to 41 ppm depending upon the endpoints examined and whether the studies were occupational or residential exposures. The residential exposure levels were noted to be about an order of magnitude less than most of the occupational exposures. The range of effects from animals chronically exposed via inhalation yields LOAELs ranging from 37 to 1000 ppm depending upon the endpoints examined. Critical data gaps are identified that have an impact on characterizing the hazard and understanding the mode of action. *Disclaimer: The views of the authors of this poster are those of the authors and do not represent Agency policy or endorsement.*

Conclusions:

Neurotoxicity in humans

- visual dysfunction (e.g., VCS & color vision)
- cognitive, deficits-visual spatial deficits,
- motor deficits

Neurotoxicity in animals

- visual functional deficits (subchronic/ electrophysiological measures)
- cognitive performance deficits (acute exposures)
- persistent motor deficits (acute developmental exposure)
- indicators of neuropathology/neurochemical change (subchronic/chronic)

Data Gaps:

- Lack of cognitive and visuo-spatial functional testing in both developmentally-exposed animals and adult animals with chronic exposure.
- Limited information on susceptible sub-populations.
- Limited assessment of exposure in some occupational studies.
- Data gaps exist in dose-response characterization, especially for low dose extrapolation in both animals and humans.
- Assumptions are made for blood levels of parent compound being the dose metric for chronic neurological effects.

Future Research Needs:

Develop chemical specific studies to reduce uncertainties for vulnerable life stages.

Refine and apply meta-analysis methods for measures of neurological functional across studies and across endpoints in the same functional domain.

Background on Tetrachloroethylene (PERC):

Common solvent used in the dry cleaning of clothes and as a metal degreaser.

An environmental contaminant of concern to EPA's air, water, and Superfund programs.

Found at many Superfund sites including those at federal facitlties.

PERC has adverse non-cancer health effects on the liver, kidney, central nervous system, reproductive system, and developing fetus in animals and humans.

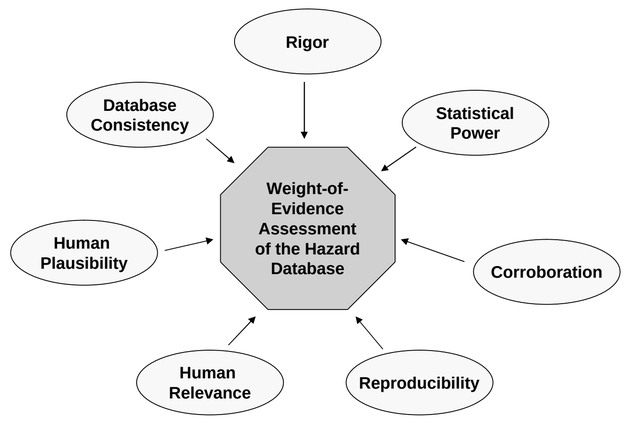
The most sensitive effects observed in humans are neurological effects, including decrements in vision or visuo-spatial function and cognitive effects.

Human studies

Residents living in close proximity to dry cleaning establishments and occupational exposure are of concern. Epidemiological studies for both of these scenarios exist.

Rodent studies

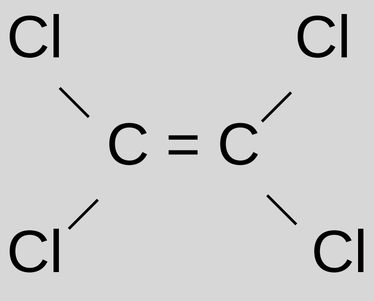
Decrements in cognition and visual function from acute exposures in rodents have been observed.



Subjects	Exposure	Effects	Author(s)
Residents near perc dry cleaning facilities, 14 exposed and 23 age- and gender-matched nonexposed controls	0.7 ppm (mean), IA (7-day monitoring period), B, 10.6 years	Increase in simple reaction time Decrements in continuous performance and visuo-spatial function No fine motor function deficits	Altmann, et al. (1995)
35 perc dry cleaners, 39 age- and education-matched controls	8 ppm TWA, IA, grab sample Mean duration of employment not reported	Increase in vocal reaction time to visual stimuli Concentration-response relationship	Spinatonda et al. (1997)
101 perc dry cleaners (both sexes), 84 nonexposed controls	Low-exposure group: 12 ppm TWA, IA, PM, 11.8 years High-exposure group: 53 ppm TWA IA, PM, 10.6 years	Decrease in information processing speed (perceptual threshold, choice reaction time), visual scanning (cancellation dZ test), visuo-spatial function No fine motor function deficits Neurological signs	Seeber (1989)
Perc dry cleaners, 60 females and 30 nonsolvent-exposed controls	15 ppm IA, 10.1 years	Impaired performance on three tests (simple reaction time, vigilance, stress) No fine motor function deficit No effects on digit symbol test	Ferroni et al. (1992)
65 perc dry cleaners, no unexposed group	11 ppm, 23 ppm, 41 ppm, PM, 1.2 to 14.6 years	Statistically significant differences between “high” and “low” lifetime exposure groups in three tests of visuo-spatial function No effect on digit span test	Echeverria et al. (1995)
30 patients with solvent-induced encephalopathy	Several solvents, including perc, 20 years	No peripheral neuropathy	Albers et al. (1999)
22 perc dry cleaners, 13 ironers, 35 controls	Mean TWA = 6 ppm (7 ppm, dry cleaning workers; 5 ppm, ironers), PM, 8.8 years (exposed subjects)	CCI statistically significantly elevated among dry cleaners with a statistically significant exposure (TWA)-response relationship. No effect on CCI in ironers	Cavalleri et al. (1994)
33 perc dry cleaners and ironers, self control (follow-up of Cavalleri et al., 1994, subjects)	Group A, 4 ppm, PM Group B, 0.7 ppm, PM	Worse CCI in subjects who experienced a higher mean TWA exposure than that reported in Cavalleri et al. No impairment in CCI in subjects who experienced a lower mean TWA exposure than that reported in Cavalleri et al.	Gobba et al. (1998)
24 solvent-exposed workers and 24 controls	Past use of solvent mixture, including perc (10%) for at least 3 years, solvent exposure for 6 years average	Color vision impairment ($p<0.05$) among exposed subjects as compared with controls	Muttray et al. (1997)
Apartment residents living above perc dry cleaning facilities: 17 exposed and 17 age- and gender-matched unexposed controls	0.4 ppm (mean, monitoring taken before closure of dry cleaners) IA, PM, B, U Duration of residence, 6 years (mean)	No effects on visual acuity or color discrimination (comparison of group means) Lower (worse) scores on tests of visual contrast sensitivity	Schreiber et al. (2002)
Employees of a day care facility located in the same building as a perc dry-cleaning business, 9 exposed and 9 age- and gender-matched unexposed controls	0.32 ppm (mean, monitoring taken before closure of dry cleaners) IA No information on duration of employment	No effects on visual acuity color discrimination (comparison of group means) Lower (worse) scores on tests of visual contrast sensitivity	Schreiber et al. (2002)
24 dry cleaners exposed to perc, 33 subjects nonoccupationally exposed to other solvents	Mean TWA = 21 ppm, PM Mean duration of exposure = 6 years	Statistically significant differences for simple reaction time and critical flicker fusion	Lauwerys et al. (1983)
56 perc- exposed dry cleaning workers, 69 non-exposed factory controls	Geometric mean TWA = 20 pm, PM Mean duration of exposure = 3 years	Statistically significant increase in the prevalence of several CNS symptoms such as nasal irritation and dizziness	Cai et al. (1991)
64 perc dry cleaners exposed to perc, 120 controls	Mean duration of employment not reported Geometric mean = 15 ppm (males), 11 ppm; (females), PM	No statistically significant differences between exposed and controls in color vision loss	Nakatsuka et al. (1992)
45 perc dry cleaners matched to 69 laundry workers, 59 pressers or counter clerks	<0.2 ppm, 3 ppm, 9 ppm, PM, 2.6 to 11 years	Statistically significant association between chronic lifetime perc exposure and reduced test performance on three cognitive tests: switching, pattern memory, and pattern recognition.	Echeverria et al. (1994)

Subjects	NOAEL/LOAEL (ppm)	Effect	Authors
F344 rats Pilot study: male 10/dose Follow-up study: males and females 12/sex dose	0, 800, 4 days, 6 hr/d 50, 200, 800, 13 wks, 6 hr/d, 5 d/wk	Changes in FEP, SEP, EEG Increased amplitude and latency in late component of FEP	Mattsson et al. (1998)
NMRI mice, males	90, 3,600 1 hr	Increase in motor activity	Kjellstrand et al. (1985)
Swiss OF1 mice, males 10/dose	596, 649, 684, 820 4 hrs	Decrease in duration of immobility	De Ceaurriz et al. (1983)
SD rats, pregnant females 13–21 litters/dose males and female Offspring assessed	0, 100, 900 on GD 7–13 or on GD 14–20 7 hr/d	Decreased weight gain Behavioral changes, more extensive for late pregnancy exposure Decreased brain acetylcholine	Nelson et al. (1980)
SD rats, males 8/dose	300, 600, 4 or 12 wks continuous (24 hr/d)	Reduced brain weight, DNA, protein	Wang et al. (1993)
SD rats, males 10/dose	200, 4 days	Decrease in brain RNA, increase in brain cholinesterase and increase motor activity	Savolainen et al. (1977a, b)
SD rats, males 5–6/dose	320, 12 wks continuous (24 hr/d), 30-day washout period 320, 4 wks continuous (24 hr/d)	Change in fatty acid composition of cerebral cortex	Kyrklund et al. (1990, 1988)
SD rats, males 5–6/dose	200, 400, 800, 4 wks continuous (24 hr/d)	Neurotransmitter changes, brain regions	Honma et al. (1980a, b)
Mongolian gerbils, males and females 6/sex/dose	60, 300, 12 wks, continuous (24 hr/d) 16-week washout period	Decrease in DNA, frontal cortex Decrease in brain weight	Rosengren et al. (1986)
Mongolian gerbils, gender unspecified	60, 12 wks, continuous (24 hr/d)	Decrease in DNA, frontal cortex Decrease in brain weight	Karlsson et al. (1987)
Mongolian gerbils, males and females 8/sex/dose	120, 12 mos continuous (24 hr/d)	Taurine, glutamine changes in brain regions	Briving et al. (1986)
Mongolian gerbils, gender unspecified 6/dose	320, 12 wks continuous (24 hr/d)	Decrease in brain weight, change in fatty acids	Kyrklund et al. (1987)
Mongolian gerbils, males 6/dose	120, 52 wks continuous (24 hr/d)	Decreased brain long-chain fatty acids	Kyrklund et al. (1984)
Guinea pigs, pregnant females 3/litters/dose males and female Offspring assessed	Maximum exposure 160, GD 33 to 65 continuous (24 hr/d)	Decrease in brain stearic acid in offspring after *in utero* exposure	Kyrklund and Hagid (1991)
NMRI mice, males and females 3–8/sex dose	9, 37, 75,150 4 wks continuous (24 hr/d)	Increase in butyl cholinesterase	Kjellstrand et al. (1984)
Males and females 10/sex dose	150, 4 wks intermittent-(1, 2, 4, 8, or 16 hr/d)	Increased motor activity	Kjellstrand et al. (1984)
SD rats, multigeneration study 28 litters/dose	0, 100, 300, 1000 6 hr/d, 5 d/wk, except during mating, 6 hr/d-7 d/wk	CNS depression in first 2 wks of F1 and F2 generations, which ceased 2 hrs after daily exposures	Tinston (1994)

Species	Exposure Conditions	Range of LOAEL’s subchronic/ chronic studies (mean/medians exposure)	Cognitive Sensory Motor Biochemical Pathology
Human	Residential Chronic	0.2 -0.7 ppm	**Verbal function, cognitive function, vigilance,** **Visual contrast sensitivity** **Reaction time**
Human	Occupational Chronic	0.3 - 41 ppm	**Visuo-spatial function, information processing speed, continuous performance** **Visual contrast sensitivity, color vision deficits** **Reaction time**
Animal studies	Experimental subchronic-chronic	37 -800 ppm	**Sensory Evoked potentials** **Butyryl cholinesterase, Brain changes: protein, DNA conc. Brain fatty acid.**



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